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Research Article

Use of Paired Test in Management of Thyroid Disorders

Tofail Ahmed[1*], Hajera Mahtab[1], Tania Tofail[2], AHG Morshed[3], Shahidul A Khan[3]

[1]Department of Endocrinology, Bangladesh Institute for Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders, Dhaka, Bangladesh;[2]Department of Endocrinology, Bhangabando Sheikh Mujibur Medical University, Dhaka, Bangladesh;[3]Endocrinology Laboratory, Diabetic Association of Bangladesh, Dhaka, Bangladesh

ABSTRACT

Aim and methods: This study is to explore utility of paired FT_4 and TSH test as a tool to classify functional status of Thyroid. We classified 58166 paired test results into the all 9 possible classes and determined frequency of class; reference ranges of FT_4 and TSH for class, their mean differences (MD) between classes and pattern of association in class and in their cohorts.

Results: FT_4 and TSH of Euthyroid class (43242) are (14.65 to 14.70 pmol/ml) and (2.44 to 2.46 μIU/ml) as 95% Confidence Interval respectively and there is no association between them (r-.049; sig.000). Major bulk of abnormal thyroid function (98.26%) is constituted by 4 classes of primary category–namely Primary Hypothyroid, Primary Hyperthyroid, Compensated Hypothyroid and Compensated Hyperthyroid. These 5 classes have significant correlation between their FT_4 and TSH (sig. of r .000) and their hormones levels are different among all classes (sig. of MDs .000). The rest 4 classes of secondary category – namely Secondary Hypothyroid, Secondary Hyperthyroid, Isolated Hypothyroximia and Isolated Hyperthyroximia are rare, correlations between their hormones are not significant in any class (sig. of r ≥.063) and all hormones are not different among all classes of this category. Cohort analysis supported the findings on correlations. So, during classification the tool exploits Thyro-pituitary axis status and its euthyroid and all 4 classes of primary category have homogenous thyro-pituiary feedback control.

Conclusion: Paired Test defines 9 classes with class specific correlation pattern between FT_4 and TSH and their ranges. We opine to use this tool; because in diagnostic setting it will reduce the burden of etiological investigations to a few for a class and in follow-up setting use of the reference range of FT_4 of the Euthyroid class as the biochemical target of treatment will ensure a cost effective strategy in Thyroid medicine.

Keywords: Thyroid function tests; FT_4; TSH; Paired test; Classification; Correlation; Cohen's standard and cohort

INTRODUCTION

The magnitude and impact of thyroid disorders on physical and mental health of human being has made Thyroid Health a public health issue. Iodine Deficiency Disorders (IDD) interventions made remarkable changes in thyroid disease patterns [1]. Introduction of sensitive newer thyroid hormone assay has brightened the scope of early detection of derangement in its functional status. We need to use appropriate tool to ascertain functional status of individuals. The functional status of one individual may shifts from one to another by natural history of a disease and/or by therapeutic interventions(s). We have published our work on paired FT_4 and TSH test where we reported that the tool enables us to differentiate healthy status from 4 common (Primary category) and 4 uncommon (Secondary category) abnormal functional status/class [2-5]. Each class has its own specific hormone ranges and pattern of correlation between them. Our present work is an extension of previous one with larger population (adding cases) along with cohort analysis. We utilized both FT_4 and TSH hormones from single sample and classify a population of 58166 tests of our laboratory and a total of 11 cohorts are analyzed to understand the class character in terms of their thyro-pituitary status and normograms of hormones.

AIM AND OBJECTIVE

Primary aim

To understand the utility of Paired Test of FT_4 and its tropic hormone TSH in assessment functional status of thyroid of population with or without treatment.

Correspondence to: Ahmed T, Department of Endocrinology, Bangladesh Institute for Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders, Dhaka, Bangladesh; E-mail: tofail.ahmed@yahoo.com

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Specific aim

A. To define classes of thyroid functional status and their frequency by Paired FT_4 and TSH Test in our laboratory.

B. To determent the reference ranges FT_4 and TSH for all classes defined paired test.

C. To compare FT_4 and TSH of different classes.

D. To evaluate the correlation between FT_4 and TSH in each class.

MATERIALS AND METHODS

We have studied 58166 paired tests in the Endocrine Laboratory of BIRDEM done by Chemiluminescent Micropartical Immunoassay (CIMA) from 01/01/2017 to 31/12/2019.

The primary variables used in the study are age, sex; FT_4 and TSH.

A. Age is grouped in a. Neonate (<1 month); b. Infant (1 month to 12 months); c. Child (>1 year to 18 years) and d. Adult (>18 years)

B. Values of FT_4 and TSH are grouped into a. Normal (within reference range); b. Low (bellow reference range) and c. High (above reference range).

a. The reference range of FT_4 is 9.14 to 23.18 (in pmol/ml)

b. The reference range of TSH (Age group based) is for i. Adult 0.47 to 5.01; ii. Child 0.37 to 6.0; iii. Infant 0.52 to 16.0 and iv. Neonate 1.30 to 16.0 (in µIU/L).

C. The 5 data series are labeled according to time of data collection: series 1 from 01/01/2017 to 31/12/2017; series 2 from 01/01/2018 to 30/06/2018; series 3 from 01/07/2018 to 31/12/2018; series 4 from 01/01/2019 to 30/06/2019; and series 5 from 01/07/2019 to 31/12/2019.

D. By combining laboratory reference values of FT_4 and TSH the study population is divided into 9 classes (nomenclature is on biochemical consideration only) (Figure 1).

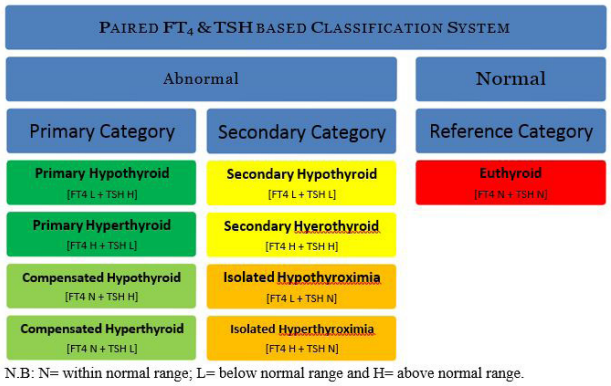


Figure 1: Paired based classification of thyroid functional status class and category.

Class 1: (FT_4 normal+TSH: normal)/Normal or euthyriod Class 2 (FT_4 low+TSH high): Primary Hypothyroidism Class 3 (FT_4 high+TSH low): Primary Hyperthyroidism

Class 4 (FT_4 normal+TSH high: Compensated Hypothyroidism Class 5 (FT_4 normal+TSH low): Compensated Hyperthyroidism. Class 6 (FT_4 low+TSH low): Secondary Hypothyroidism.

Class 7 (FT_4 high+TSH high): Secondary Hyperthyroidism Class 8 (FT_4 low+TSH normal): Isolated Hypothyroximia Class 9 (FT_4 high+TSH normal): Isolated Hyperthyroximia.

E. The reference range FT_4 and TSH are determine as the 95% Confidence Interval and compared between the classes by independent sample t tests.

F. Correlation between FT_4 and TSH with of total; 9 class and Cohorts available for each class are determined by bivariate correlations and association is expressed by Cohen's standard (r value<0.1 means no association between the 2 variables, 0.1 to <0.3 weak association; 0.3 to <.0.5 moderate association and >.0.5 strong association). Total 11 cohorts-4 for age groups (Adult >18 year); children >1 to <19); Infant >1 month-1 year and neonate up to 1 month); 2 for sex groups (male and female) and 5 for data series (series 1 to 5) (Figure 2).

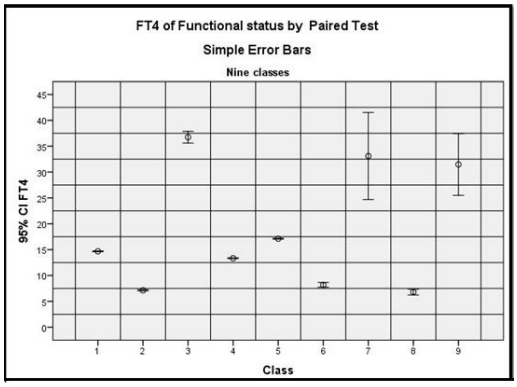


Figure 2: FT_4 a class are distinct from any other class in 33 out of total 36 settings of comparisons. Among 5 class (1-5) they are all distinct (sig. of MD .000).

G. Inclusion and exclusion criteria: All paired test done in our laboratory during the period 01/01/2017 to 31/12/2019. These included samples from same person but in different time points for follow-up are included. And test results those are above or below the detection range of assay kit are excluded.

H. Hormone assay methods. The ARCHITECTURE Free T_4 and TSH assay kit of Abbott were used. They determine Free T_4 and TSH in human serum and plasma by two-step immunoassay by CMIA technology.

I. SPSS (Version IBM 24) is used for analysis.

DISCUSSION

The thyroid medicine is facing some pitfalls of thyroid function tests interpretations [6-10]. We explore the features of classes defined by combining FT_4 and TSH tests results from same blood sample in diagnostic as well as in follow up settings. If classes defined by this system can show significantly different hormone profiles from one another, than the paired test will be a valid tool to determine the functional status. The TSH test gained much attention soon after its assay kits became available. A preexisting concept of a negative feedback control between Thyroid and Pituitary has contributed to place TSH test over Thyroxin test. Still the debate of "Which one is better-TSH or FT_4?" is going on. Now a day's, some group uses TSH test as a screening test for all (?) thyroid dysfunctions and also to judge the adequacy of replacement and antithyroid drug treatment [9,10]. Ideally, a perfect negative linear relationship between FT_4 and TSH can only rationalize such a dictum. We have published our work on this issue [2-5] and the current work is with more data with cohort analysis.

We classified 58166 tests of our laboratory into all possible classes by permutation and combinations of their FT_4 and TSH results. This system yields a total of 9 classes. They are Euthyroid with normal thyroid function and 4 pairs of abnormal functions–a) Primary Hypothyroid and Primary Hyperthyroid; b) Secondary Hypothyroid and Secondary Hyperthyroid; c) Compensated Hypothyroid and Compensated Hyperthyroid and d) Isolated Hypothyroximia and Isolated Hyperthyroximia.

The correlation between the 2 hormones for total population (weak negative) changed to a class specific form by our tool. In the healthy or euthyroid class it is in the grade of no correlation; 4 classes of primary category, who covers most cases of abnormal functional status (>98%), have significant correlation (sig. of r .000) of different grades; no correlation in Compensated Hypothyroid; weak negative in Compensated Hyperthyroid and moderate negative in Primary Hypothyroid and Primary Hyperthyroid. And 4 classes of secondary category, which covers very small proportion of abnormal functional status (<2%), have no significant correlation (sig. of r>.063). These observations are supported by cohort analysis. Therefore, our tool classifies the population on the basis of the functional status thyro-pituitary axis of individual subject.

Hormones of a class are significantly different from each of those of the other classes when it is considered among 5 classes and all of them have significant correlations (Class 1–5). But this is not applicable for 4 classes (class 6–9) of secondary category. Therefore, we can conclude that the paired test effectively separate the rare cases from the common ones and divide them into 4 different classes-all of them are with heterogenous thyro-pituitary functional status. The rest 5 classes have homogenous thyro-pituitary functional status and distinct FT_4 and TSH.

Most of the nomenclatures of classes of this system are already in use in existing practice but they are not interchangeable with that of the new one, because of our diagnostic criteria for a class is based on paired FT_4 and TSH result from a single blood sample. The two classes-Compensated Hypothyroid and Compensated Hyperthyroid are popularly known as Sub-clinical Hypothyroid and Sub-clinical Hyperthyroid respectively. We avoid terminology 'Sub-clinical' because our tool is a biochemical one.

The reference population for normal functional status is euthyroid class. Its population size is 74.3% (43242) of our total study population. This population consists of healthy thyroid status plus cases treated to target and they are likely having healthy thyropituitary feedback axis. Their FT_4 and TSH are (14.65 to 14.70) and (2.44 to 2.46) respectively and both are in mid zone of their reference ranges. The correlations between their FT_4 and TSH in all but in 1 cohort out total 11 are in the same grade i.e. no correlation. We have also documented no correlation between FT_4 and TSH in class 4 – Compensated Hypothyroid; its FT_4 is adjacent to that of Euthyroid within euthyroximia. In our previous work we have postulated that there exists a silent phase thyropituitary feedback control when their FT_4 is within euthyroximia [2-5].

Primary Hypoththyroism (Class 2) and Primary Hyperthyroidsm (Class 3) have FT_4 are beyond the reference value on either sides and both are having moderate negative association between their FT_4 and TSH. In the dsease list for such functional status Autoimmune Thyroid Disorders (Hashimoto's disease or Grave's disease) comes first followed by the nodular hyperfunctions (Single or Multinodular) or de Quervain's thyroiditis etc for the Primary Hyperthyroid only [11-18].

The FT_4 of Compensated Hypothyroidism and Compensated Hyperthyroidism classes are within euthyroxima and are on either side of that for Euthyroid class. The association pattern of Compensated Hypothyroidism is similar to Euthyroid but that of Compensated Hyperthyroidism is similar to Primary Hyperthyroid (Tables 1 and 2). Therefore, it may be postulated that Compensated Hyperthyroid cases shifts to and from Primary Hyperthyroid more frequently whereas Euthyroid cases shifts to and from Compensated Hypothyroid more frequently. We are convinced that shift phenomenon of functional status is more frequently between adjacent pair of classes and are due to the natural history of disease or result of therapeutic intervention.

The Secondary Hypothyroidism and Secondary Hyperthyroidism are two well recognize terminology/class of thyroid dysfunction. The first one is in fact historically represented by Sheehan's syndrome for more than 100 years and now it includes others cases such as post-surgery at sellar and parasellar regions, post radiation of head, head injury etc [19-24]. The second one-Secondary Hyperthyroidism is loosely termed as Thyroid Hormone Resistance Syndrome now getting expansion with some rare challenging disorders like TSHomas, genetically determined hormone receptor abnormality etc [25-29]. The correlation we documented in our study is not significant for this pair of class and it grade charges in their cohorts. We believe, this is not only due to smaller population size but for the heterogeneity of diseases those constitute such functional statuses.

The two new classes identified by this system of classification are Isolated Hypothyroximia and Isolated Hyperthyroximia. They are de novo classes of paired test based classification system and belong to secondary category. Their FT_4 are (6.24-7.35) and (25.49-37.43) respectively and they do not differ significantly from the respective primary hypo/hyper (sig. of MDs >.072).

There is no association between their FT_4 and TSH. We assume that their cases are likely to shift between their respective primary hypo/hyper status and euthyroid status. All cases of the classes should be screened for autoimmune thyroid diseases. Their population sizes are small in our series and there is also a need for more cases to validate the class features. Our secondary category classes constitute very small proportion of abnormal thyroid function (approximately 1.85%). We opine to follow a policy by the laboratory to perform a routine repeat assay of hormones for these small but important group/classes.

This system of classification has the capability of labeling every single paired test report to a class (360^0 capability). This has the potentiality to solve many pitfalls exist with the current practice especially on Non thyroidal illness, sick euthyroid etc because it can provide clue on aetiology and phenomenon of shift of functional status. At diagnostic setting aetiological investigations can be prioritized and minimized. For example initial test for a case with hypothyroximia (Class 2,4 and 6) should be screening for AITD; test for a case with hyperthyroximia (Class 3,5 and 7) should be screening for AITD first and then screening for hyper functioning nodule(s) by RAI scan [30-32] and for any case of class 6 and 7 clinical audit and then appropriate investigation such as advance imaging, dynamic hormone study or molecular diagnosis can be slected carefully. For remaining classes (Class 1,8 and 9) screening for AITD and a follow-up plan is necessary because a functional status of an individual can shift to another one both on natural courses as well by therapeutic intervention [26,27]. We need to

do study on aetiological distribution of cases for these new classes now. Such data will help us to understand the phenomenon of status shift of disease. And thereby the clinicians will be able to take appropriate management policy for their cases in time.

As we have documented 'no strong linear negative relation between FT_4 and TSH in total or in any of its class (-.490 to+.308)', we are unable to support the current practice of only TSH test neither as a screening test nor to judge the adequacy of replacement/antithyroid drug treatment. Rather targeting to keep FT_4 within the range our euthyroid class will provide opportunity of doing only FT_4 test in follow up setting of all abnormal thyroid function classes. Such an approach will not only reduce many pitfalls but also make lifelong thyroid care cost effective. The importance of a sensitive dependable biochemical test for functional status is rising because there is a sharp increase in number of test among asymptomatic person. For example executive health checkup programs and long term or lifelong follow-up for persons with thyroid dysfunction who are also mostly asymptomatic. Health checkup for increasing population with growth or fertility problems and cancer survivor are also included in this list.

We once again urge that all endocrine laboratories to publish their paired test based normograms of the new 9 classes; and clinicians to utilize them for diagnosis and use the range of FT_4 of euthyroid as the treatment target for all cases with abnormal thyroid function. We firmly believe, such an endeavor will bring down the investigation cost and improve Thyroid Medicine as whole by reducing many pitfalls.

RESULTS

Our study population consists of 58166 paired serum FT_4 and TSH test reports of our laboratory from 01/01/2017 to 31/12/2019. Case distributions by age group they are Adult 46741 (80.36%); Children 8327 (14.32%); Infant 2219 (3.81%) and Neonate 879 (1.51%); by Sex 17254 (29.7%) Male and 40912 (70.3%) Female and by data series-series 1-11864 (20.4%); series 2-10730 (18.4%); series 3-11522 (19.8%); series 4-11506 (19.8%) and series 5-12544 (21.6%). We considered all these 11 as cohorts for our analysis (Table 1).

FT_4 (in pmol/ml): mean 14.97; median 14.31; Std. Deviation 4.98; SE of mean+0.02; range (0.09 to 184.09) and 95% CI (14.93 to 15.01). TSH (in μUI/ml): mean 3.88; median 2.30; Std. Deviation 9.42; SE of mean+0.04; range (0.00 to 184.44) and 95% CI (3.81 to 3.96). r value between them is-.246 (sig. .000) which is weak negative correlation by Cohen's grading and this grade remained same in all the 11 cohorts (Table 2 and Figures 3-5).

Table 1: Frequency distribution of classes by paired test and their cohorts.

		Euthyroid		Primary category				Secondary category			
		Class 1	Class 2	Class 3	Class 4	Class 5	Class 6	Class 7	Class 8	Class 9	Total
Total		43242	1151	930	6916	5667	50	37	103	70	58166
		-74.30%	-2.00%	-1.60%	-11.90%	-9.70%	-0.09%	-0.06%	-0.18%	-0.12%	-100%
Cohorts on age	Adult	33741	960	823	6232	4800	45	33	88	19	46741
	(>18 Yr.)	-78.00%	-83.40%	-88.50%	-90.10%	-84.70%	-90.00%	-89.20%	-85.40%	-27.10%	-80.40%
	Children	6879	153	59	678	530	3	4	11	10	8327
	(1-18 Yr)	-15.90%	-13.30%	-6.30%	-9.80%	-9.40%	-6.00%	-10.80%	-10.70%	-14.30%	-14.30%
	Infant	1937	27	36	1	190	1	Nil	2	25	2219
	1 M-	-4.50%	-2.40%	-3.90%	-0.01%	-3.40%	-2.00%		-1.90%	-35.70%	-3.80%
	12 M.)										
	Neonate	685	11	879	5	147	1(2.0%)	Nil	2	16	879
	(Upto 4 W)	-1.60%	-1.00%	-1.50%	-0.07%	-2.60%			-1.90%	-22.90%	-1.50%
Cohorts on sex	Male	13337	398	274	1670	1474	19	17	30	35	17254
		-30.80%	-34.60%	-29.50%	-29.70%	-26.00%	-38.00%	-29.70%	-29.10%	-50.00%	-29.70%
	Female	29905	753	656	5246	4193	31	20	73	35	40912
		-69.20%	-65.40%	-70.50%	-70.30%	-74.00%	-62.00%	-70.30%	-70.90%	-50.00%	-70.30%
Cohorts on data	Series1	8694	267	199	1588	1070	6	4	23	12	11864
		-20.10%	-23.20%	-21.40%	-23.00%	18.90%	-12.00%	-10.80%	-22.30%	-17.10%	-20.40%
	Series2	7772	214	157	1665	857	17	13	20	15	10730
		-18.00%	-18.60%	-16.90%	-24.00%	-15.10%	-34.00%	-35.10%	-19.40%	-21.40%	-18.40%
	Series3	8256	261	208	1617	1115	14	13	20	18	11522
		-19.10%	-22.70%	-22.37%	-23.40%	-19.70%	-28.00%	-35.10%	-19.40%	-25.70%	-19.80%
	Series4	11506	204	162	1082	1135	5	8	19	10	11506
		-19.80%	-17.70%	-17.40%	-15.6	-20.00%	-10.00%	-16.00%	-18.40%	-14.30%	-19.80%
	Series5	12544	205	204	964	1489	5	2	21	15	12544
		-21.60%	-17.80%	-21.90%	-13.90%	-26.30%	-10.00%	-4.50%	-20.40%	-21.40%	-21.60%

Inference: Primary category classes constitute more than 98% of cases with abnormal functional status. Adult and female predominate in all classes except in isolated hyperthyroximia (Class 9) where not particular age and sex are predominant.

Table 2: Correlation Between FT_4 and TSH in class by paired test and their cohorts.

	Reference	Primary category				Secondary category				Total
	Class 1	Class 2	Class 3	Class 4	Class 5	Class 6	Class 7	Class 8	Class 9	
Total	-0.049	-0.49	-0.349	-0.049	-0.211	0.165	0.308	-0.023	-0.031	-0.246
	(sig..000)	(sig..000)	(sig..000)	(sig..000)	(sig..000)	(sig..251)	(sig..063)	(sig..815)	(sig..800)	(sig..000)
	[43242]	[1151]	[930]	[6916]	[5667]	[50]	[37]	[103]	[70]	[58166]
Adult (>18 years	-0.088	-0.529	-0.42	-0.059	-0.253	0.097	0.534	-0.234	0.288	-0.245
	(sig..000)	(sig..000)	(sig..000)	(sig..000)	(sig..000)	(sig..527)	(sig..001)	(sig..028)	(sig..232)	(sig..000)
	[33741] a1	[960] b1	[823] a1	[6232] a1	[4800] a1	[45] b2	[33] b1	[88] b1	[19]c2	[46741]
Children (>1 to 18 years)	-0.022	-0.278	-0.508	-0.054	-0.124	-0.15	-0.499	-0.656	-0.438	-0.271
	(sig..070)	(sig..001)	(sig..158)	(sig..158)	sig..004)	(sig..904)	(sig..056)	sig..029)	(sig..205)	(sig..000)
	[6879] a2	[153] b1	[59] b1	[678] a2	[530] a1	[3] c2	[4]c2	[11] b1	[10] b2	[8327]
Infant (1 to 12 months)	-0.041	-0.568	-0.312	[1]	-0.268	[1]	[0]	[2]	-0.249	-0.276
	(sig..072)	(sig..002)	(sig..064)		(sig..000)				(sig..814)	(sig..000)
	[1938] a2	[27] b1	[36] a2		[188] a1				[25] b2	[2218]
Neonate (<1 month)	-0.103	-0.886	-0.55	-0.345	0.078	[1]	[0]	[2]	-0.132	-0.228
	(sig..007)	sig..000)	(sig..064)	(sig..569)	(sig..345)				(sig..627)	(sig..000)
	[685] b1	[11] b1	[12] b2	[5] c2	[147]c2				[16] b2	[879]
Male	-0.017	-0.449	-0.355	-0.008	-0.208	0.284	-0.041	0.004	-0.12	-0.252
	(sig..044)	(sig..000)	(sig..000)	(sig..735)	(sig..000)	(sig..239)	(sig..875)	(sig..982)	sig..492)	(sig..000)
	[13337] a1	[398] a1	[273] a1	[1670] a2	[1474] a1	[19] a2	[17] c2	[30] a2	[35] b2	[17254]
Female	-0.08	-0.511	-0.35	-0.07	-0.212	0.078	0.541	-0.101	0.72	-0.244
	(sig..000)	(sig..000)	(sig..000)	(sig..000)	(sig..000)	(sig..676)	(sig.014)	(sig..393)	(sig..683)	(sig..000)
	[29905] a1	[753] b1	[657] a1	[5246] a1	[4193] a1	[31] N2	[20] b1	[73] b2	[35]c2	[40912]
Series 1	-0.041	-0.149	-0.488	-0.129	-0.166	0.462	-0.417	-0.352	-0.075	-0.257
	(sig..000)	(sig..015)	(sig..000)	(sig..000)	(sig..000)	(sig..357)	(sig..583)	(sig..099)	(sig..817)	(sig..000)
	[8694] a1	[267] b1	[199] a1	[1588] b1	[1071] a1	[6] b2	[4]c2	[23]c2	[12] a2	[11864]
Series 2	-0.028	-0.459	-0.377	-0.044	-0.177	0.089	-0.14	0.07	-0.033	-0.256
	(sig..013)	(sig..000)	(sig..000)	(sig..071)	(sig..000)	(sig..735)	(sig..647)	(sig..768)	(sig..906)	(sig..000)
	[7772] a1	[214] a1	[157] a1	[1665] a2	[857] a1	[17] b2	[13]c2	[20]a2	[15] a2	[10730]
Series 3	-0.091	-0.7	-0.347	-0.042	-0.268	0.517	0.753	0.074	-0.356	-0.268
	(sig..000)	(sig..000)	(sig..000)	(sig..094)	(sig..000)	(sig..059)	(sig..003)	(sig..757)	(sig..147)	(sig..000)
	[8256] a1	[261] b1	[208] a1	[1617] a2	[1115] a1	[14] b2	[13] b1	[20]a2	[18] c2	[11522]
Series 4	-0.045	-0.73	-0.388	-0.097	-0.25	-0.247	0.037	-0.046	0.029	-0.254
	(sig..000)	(sig..000)	(sig..000)	(sig..001)	(sig..000)	(sig..556)	(sig..953)	(sig..851)	(sig..936)	(sig..000)
	[8881] a1	[204] b1	[162] a1	[1082] a1	[1135] a1	[8]c2	[5] c2	[19] a2	[10] a2	[11506]
Series 5	-0.018	-0.662	-0.273	-0.033	-0.196	0.304		-0.037	0.033	-0.208
	(sig..072)	(sig..000)	(sig..000)	(sig..309)	(sig..000)	(sig..618)	[2]	(sig..875)	(sig..906)	(sig..000)
	[9639] a2	[205] b1	[204] b1	[964] a2	[1489] a1	[5] a2		[21] a2	[15]a2	[12544]

Inference: Classes of reference and primary category have significant correlation and also in most (42 out of 54) of their cohorts have significant correlation in the same or an adjacent grade of their class. In secondary category classes correlations are not significant and most (22 out of 37) of their cohorts not significant and in a different grade.

N.B.: a=in same grade for its class; b=in an adjacent grade for its class; c=in a different grade than its class. 1=statistically significant and 2=statistically not significant.

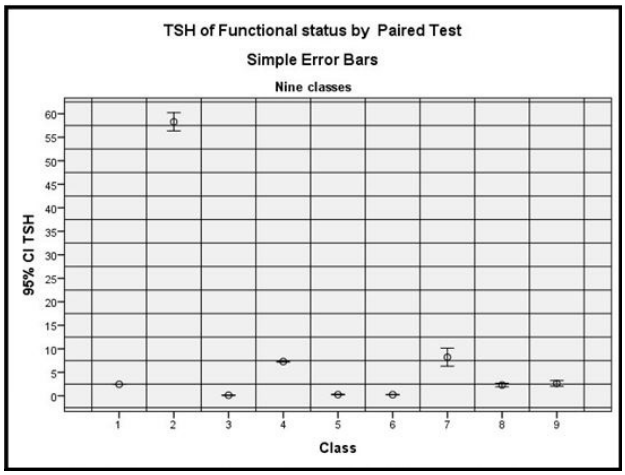


Figure 3: TSH a class are distinct from any other class in 31 out of total 36 settings of comparisons. Among 5 class (1-5) they are all distinct (sig. of MD .000).

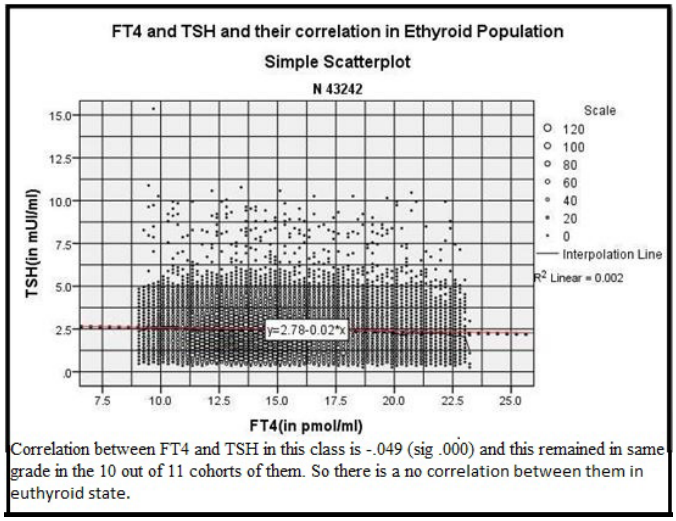


Figure 4: FT_4: Mean 14.67; SE of mean +0.01; Range (9.14 to 23.17) and 95% CI (14.65 to 14.70). TSH: Mean 2.45; SE of mean +0.01; Range (0.32 to 15.35) & 95% CI (2.44to 2.46).

Class 2 Primary Hypothyroid FT_4(7.04 -7.24) TSH(56.34 -60.23)* r = -.490(.000) N 1151	TSH H	**Class 4** Compensated Hypothyroid FT_4 (17.02 -17.20)* TSH (7.19 -7.39) r = -.049(.000) N 6916	TSH H	**Class 7** Secondary Hyperthyroid FT_4 (24.68 -41.52) TSH (6.29-10.13) r = +.308(.063) N 37
FT_4 L		FT_4N		FT_4H
Class 8 Isolated Hypothyroximia FT_4(6.24 -7.35) TSH (1.94 – 2.68) r = -.023(.815) N 103	TSH N	**Class 1** Euthyroid FT_4(14.65 -14.70)* TSH(2.44 – 2.46) r = -.049(.000) N 43242	TSH N	**Class 9** Isolated Hyperthyroximia FT_4 (25.49 -37.43) TSH (2.14 -3.24) r = -.031(.800) N 70
FT_4 L		FT_4 N		FT_4 H
Class 6 Secondary Hypothyroid FT_4(7.73-8.65)* TSH (0.23-0.27) r = +.165(.251) N 50	TSH L	**Class 5** Compensated Hyperthyroid FT_4(17.02-17.20)* TSH (0.26-0.27) r = -.211(.000) N 5667	TSH L	**Class 3** Primary Hyperthyroid FT_4(35.61-37.88)* TSH (0.12 -0.13)* r = -.349(.000) N 930
Inference: Euthyroid and 4 classes of primary category (class 1–5) have significant correlation between their FT_4 & TSH (sig .000) and both the hormones of any of these classes is significantly different from rest 4 classes (sig of MDs .000).				
N.B: FT_4 & TSH N, L & H means normal, low & high. FT_4 (95% CI in pmol/ml); TSH (95% CI in μIU/ml) r=correlation coefficient between FT_4 & TSH [expressed in r value (2 tail significance) N] There are nine classes. *Significant Mean Difference from rest 8 classes.				

Figure 5: Class character of our study population (N 58166) by paired test based classification of functional status of thyroid.

Our tool the paired test yields nine classes.

A. The class number, nomenclatures (definition) with their %(n) are as follows:

Class 1: Normal/Euthyroid (FT_4 N+TSH N) 74.3% (43242); Class 2: Primary Hypothyroidism (FT_4 L+TSH H), 2.0% (1151); Class 3: Primary Hyperthyroidism (FT_4 H+TSH L), 1.6% (930); Class 4: Compensated Hypothyroidism (FT_4 N+TSH H), 11.9% (6916); Class 5: Compensated Hyperthyroidism (FT_4 N+TSHH), 9.7% (5667); Class 6: Secondary Hypothyroid (FT_4 L+TSH L), 0.1% (50); Class 7: Secondary Hyperthyroidism (FT_4 H+TSH H), 0.09% (37); Class 8: Isolated Hypothyroximia (FT_4 L+TSH N), 0.2% (103) and Class 9: Isolated Hyperthyroximia (FT_4 H+TSH N), 0.1% (70). So the major bulk of abnormal thyroid functional classes (98.15%) are Class 2 to 5, they are categorized as primary category. The remaining classes of secondary category and rare (Table 1).

B. The reference ranges of FT_4 (pmol/ml) and TSH (μIU/L) of class is shown as Class numbers, nomenclature with 95% Confidence Interval are as follows:

Class 1: Normal/Euthyroid (14.65–14.70) and (2.44–2.46); Class 2: Primary Hypothyroidism(7.14–7.24) and (56.34–60.23); Class 3: Primary Hyperthyroidism(35.61–37.88) and (0.12–0.13); Class 4: Compensated Hypothyroidism(13.28–13.41) and (7.19–7.39); Class 5: Compensated Hyperthyroidism (17.02–17.20) and (0.26–0.27); Class 6: Secondary Hypothyroid (7.73–8.65) and (0.23–0.27); Class 7: Secondary Hyperthyroidism (24.68–41.52) and (6.29–10.13); Class 8: Isolated Hypothyroximia (6.24–7.35) and (1.94–2.68) and Class 9: Isolated Hyperthyroximia (25.49–37.43) and (2.04–2.24) (Table 2 and Figures 3-5).

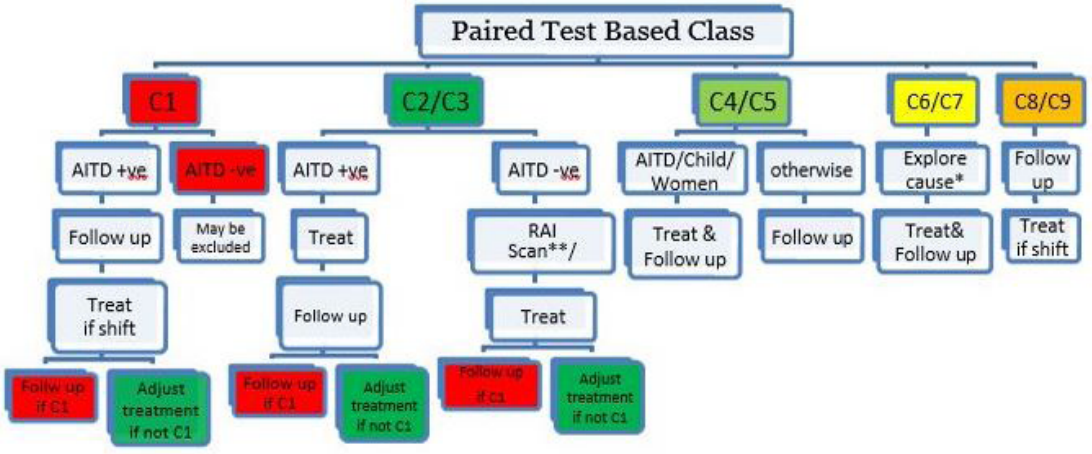
C. Comparison hormones of the between classes are as follows:

1. The reference population for healthy status is class 1 or Euthyroid. The mean differences for FT_4 of euthyroid with all the 8 abnormal classes are significant (sig..000). The mean differences for TSH with the all but 2 abnormal classes are significant (sig..000) and the exceptions is with Class 8-Isolated Hypothyroximia (sig. .279) and Class 9-Isolated Hyperthyroximia (sig. .236).

2. 2. FT_4 and TSH of a class are distinct from any other class in 33 and 31 out of total 36 settings of comparisons respectively. FT_4 and TSH of 5 classes (Class 1 – 5) are distinct among their 10 paired settings (sig. of MDs .000) and FT_4 and TSH of rest 4 classes (Class 6–9) are not distinct in one among their 6 paired settings (sig. of MDs >.334) (Figure 6).

D. Correlation study result:

Correlation between FT_4 and TSH of the all and individual classes are as follows: By Cohen's standard the association between FT_4 and TSH in all the 58166 test is a weak negative (r =-.246; sig. .000). But in class setting association changed to different grade and they are statistically significant in euthyroid and all the 4 classes of primary category (Class 1–5) (sig. .000) but not in any classes of secondary category (Class 6–9) (sig.>.063) (Table 3). There is no association (r<.1) class1: Euthyroid (n 43242) (r =-.049; sig. .000), class 4: Compensated Hypothyroidism (n 6916) (r =-.049; sig. .000), Class 8: Isolated Hypothyroximia (n 103) (r =-.023; sig. .815) and Class 9: Isolated Hyperthyroximia (n70) (r=-.031; sig. .800). Weak negative association (r>.1 to <.3) in class 5: Compensated Hyperthyroidism (n 5667) (r =-.211; sig. .000). Moderate negative association (r >.3 to <.5) in class 2: Primary Hypothyroidism (n 1151) (r =-.490; sig. .000) and Class 3: Primary Hyperthyroidism (n 930) (r =-.349; sig. .000). And weak positive association in Class 6: Secondary Hypothyroidism (n 50) (r =+.165; sig. .251) and Class 7: Secondary Hyperthyroidism (n 37) (r =+.308; sig. .063).



Inference: Paired Test bases classification system can make investigation and management strategies of Thyroid dysfunctions simplified.

N.B: C1= Euthyroid; C2=Primary Hypothyroid; C3=Primary Hyperthyroid; C4=Compensated Hypothyroid; C5=Compensated Hyperthyroid; C6=Secondary Hypothyroid; C7=Secondary Hyperthyroid; C8=Isolated Hypothyroximia and C9=Isolated Hyperthyroximia. *Hypothalamo – Pituitary-Thyroid axis by imaging (C&7) &/or dynamic hormone study (C6) and gene/molecular study (C7). **Nodular Hyperfunctioning state / low or no uptake Hyperthyroid state (C3).

Figure 6: Classification, investigation, treatment and follow up of thyroid dysfunctions by paired test.

CONCLUSION

Cohort analysis documented correlation between FT_4 and TSH in all cohorts remained in the weak negative grade for the total population (r-.276 to-.208; sig. 000). In 5 classes (Class 1-5) correlation of most cohorts remained in the same or in an adjacent grade for that of their total class. But in rest 4 classes (Class 6-9) cohorts correlations are mostly not significant and shifted to a different grade from that of their total class.

CONFLICT OF INTEREST

There is no conflict of interest to be reported by any of the authors.

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